CLAIMS

1. A method for controlling the flux of penetrants across an adaptable semi-permeable porous barrier comprising the steps of:

- preparing a formulation by suspending or dispersing said penetrants in a polar liquid in the form of fluid droplets surrounded by a membrane-like coating of one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate, provided that
- said at least two substances differ by at least a factor of 10 in solubility in said polar liquid,
- and / or said substances when in the form of homo-aggregates (for the more soluble substance) or of hetero-aggregates (for any combination of both said substances) have a preferred average diameter smaller than the diameter of homo-aggregates containing merely the less soluble substance,
- and / or the more soluble substance tends to solubilise the droplet and the content of such substance is to up to 99 mol-% of solubilising concentration or else corresponds to up to 99 mol-% of the saturating concentration in the unsolubilised droplet, whichever is higher;
- and / or the presence of the more soluble substance lowers the average elastic energy of the membrane-like coating to a value at least 5 times lower, more preferably at least 10 times lower and most preferably more than 10 times lower, than the average elastic energy of red blood cells or of phospholipid bilayers with fluid aliphatic chains,
- said penetrants being able to transport agents through the pores of said barrier or to enable agent permeation through the pores of said barrier after penetrants have entered the pores,
- selecting a dose amount of said penetrants to be applied on a predetermined area of said barrier to control the flux of said penetrants across said barrier, and

- applying the selected dose amount of said formulation containing said penetrants onto said area of said porous barrier.

2. The method according to claim 1,
characterised in that the flux across said barrier is increased by enlarging the applied dose per area of said penetrants.

3. The method according to claims 1 or 2,
characterised in that the pH of the formulation is between 3 and 10, more preferably between 4 and 9, and most preferably between 5 and 8.

4. The method according to any one of the preceding claims,
characterised in that the formulation comprises:

- at least one thickening agent in an amount that increases the formulation viscosity to maximally 5 Nm/s, more preferably up to 1 Nm/s, and most preferably up to 0.2 Nm/s, so that formulation spreading-over, and drug retention at the application area is enabled,
- and / or at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100 % per 6 months, more preferably to less than 100 % per 12 months and most preferably to less than 50 % per 12 months
- and / or at least one microbicide in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days.

5. The method according to claim 4,
characterised in that said at least one microbicide is added in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the

formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 3 days, and more preferably after a period of 1 day.

6. The method according to claim 4,
characterised in that said thickening agent is selected from the class of pharmaceutically acceptable hydrophilic polymers, such as partially etherified cellulose derivatives, like carboxymethyl-, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl- or methyl-cellulose; completely synthetic hydrophilic polymers such as polyacrylates , polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylates, polyacrylonitriles, methallyl-sulphonates, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactides, polyethylene glycol-diacrylates, polyvinylpyrrolidones, polyvinyl alcohols, poly(propylmethacrylamides), poly(propylene fumarate-co-ethylene glycols), poloxamers, polyaspartamides, (hydrazine cross-linked) hyaluronic acids, silicones; natural gums comprising alginates, carrageenans, guar-gums, gelatines, tragacanths, (amidated) pectins, xanthans, chitosan collagens, agaroses; mixtures and further derivatives or co-polymers thereof and / or other pharmaceutically, or at least biologically, acceptable polymers.

7. The method according to claim 6,
characterised in that the concentration of said polymer is in the range between 0.01 w- % and 10 w- %, more preferably in the range between 0.1 w- % and 5 w- %, even more preferably in the range between 0.25 w- % and 3.5 w- % and most preferably in the range between 0.5 w- % and 2 w- %.

8. The method according to claim 4,

characterised in that said anti-oxidant is selected from synthetic phenolic antioxidants, such as butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX, etc.), tertiary butylhydroquinone (TBHQ), propyl gallate (PG), 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ); aromatic amines (such as diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol, tetrahydroindenoindol); phenols and phenolic acids (such as guaiacol, hydroquinone, vanillin, gallic acids and their esters, protocatechuic acid, quinic acid, syringic acid, ellagic acid , salicylic acid, nordihydroguaiaretic acid (NDGA), eugenol); tocopherols (including tocopherols (alpha, beta, gamma, delta) and their derivatives, such as tocopheryl-acylate (e.g. -acetate, -laurate, myristate, -palmitate, -oleate, -linoleate, etc., or any other suitable tocopheryl-lipoate), tocopheryl-POE-succinate; trolox and corresponding amide- and thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters (e.g. 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid, etc.); non-steroidal anti-inflammatory agents (NSAIDs), such as indomethacin, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofen, ketoprofen, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital, acetaminephen); aminosalicylic acids and derivatives; methotrexate, probucol, antiarrhythmics (e.g. amiodarone, aprindine, asocainol), ambroxol, tamoxifen, b-hydroxytamoxifen; calcium antagonists (such as nifedipine, nisoldipine, nimodipine, nicardipine, nilvadipine), beta-receptor blockers (e.g. atenolol, propranolol, nebivolol); sodium bisulphite, sodium metabisulphite, thiourea; chelating agents, such as EDTA, GDTA, desferral; endogenous defence systems, such as transferrin, lactoferrin, ferritin, ceruloplasmin, haptoglobion, haemopexin, albumin, glucose, ubiquinol-10; enzymatic antioxidants, such as superoxide dismutase and metal complexes with a

similar activity, including catalase, glutathione peroxidase, and less complex molecules, such as beta-carotene, bilirubin, uric acid; flavonoids (e.g. flavones, flavonols, flavonones, flavanonals, chacones, anthocyanins), N-acetylcystein, mesna, glutathione, thiohistidine derivatives, triazoles; tannines, cinnamic acid, hydroxycinnamatic acids and their esters (e.g. coumaric acids and esters, caffeic acid and their esters, ferulic acid, (iso-) chlorogenic acid, sinapic acid); spice extracts (e.g. from clove, cinnamon, sage, rosemary, mace, oregano, allspice, nutmeg); carnosic acid, carnosol, carsolic acid; rosmarinic acid, rosmarindiphenol, gentisic acid, ferulic acid; oat flour extracts, such as avenanthramide 1 and 2; thioethers, dithioethers, sulphoxides, tetralkylthiuram disulphides; phytic acid, steroid derivatives (e.g. U74006F); tryptophan metabolites (e.g. 3-hydroxykynurenine, 3-hydroxyanthranilic acid), and organochalcogenides, or else is an oxidation suppressing enzyme.

9. The method according to claim 8, **characterised in that** the concentration of BHA or BHT is between 0.001 and 2 w-%, more preferably is between 0.0025 and 0.2 w-%, and most preferably is between 0.005 and 0.02 w-%, of TBHQ and PG is between 0.001 and 2 w-%, more preferably is between 0.005 and 0.2 w-%, and most preferably is between 0.01 and 0.02 w-%, of tocopherols is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.075 w-%, of ascorbic acid esters is between 0.001 and 5, more preferably is between 0.005 and 0.5, and most preferably is between 0.01 and 0.15 w-%, of ascorbic acid is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.1 w-%, of sodium bisulphite or sodium metabisulphite is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01-0.15 w-%, of thiourea is between 0.0001 and 2 w-%, more preferably is between 0.0005 and 0.2, and most preferably is between 0.001–0.01 w-%, most typically 0.005 w-%, of cystein is

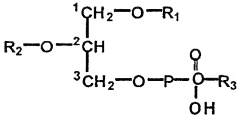
between 0.01 and 5, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1 and 1.0 w-%, most typically 0.5 w-%, of monothioglycerol is between 0.01 and 5 w-%, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1-1.0 w-%, most typically 0.5 w-%, of NDGA is between 0.0005-2 w-%, more preferably is between 0.001–0.2 w-%, and most preferably is between 0.005-0.02 w-%, most typically 0.01 w-%, of glutathione is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.2 w-%, most typically 0.1 w-%, of EDTA is between 0.001 and 5 w-%, even more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.2 w-%, most typically between 0.05 and 0.975 w-%, of citric acid is between 0.001 and 5 w-%, even more preferably is between 0.005 and 3 w-%, and most preferably is between 0.01-0.2, most typically between 0.3 and 2 w-%.

10. The method according claim 4, **characterised in that** said microbicide is selected from short chain alcohols, such as ethyl and isopropyl alcohol, chlorbutanol, benzyl alcohol, chlorbenzyl alcohol, dichlorbenzylalcohol; hexachlorophene; phenolic compounds, such as cresol, 4-chloro-m-cresol, p-chloro-m-xylenol, dichlorophene, hexachlorophene, povidon-iodine; parabens, especially alkyl-paraben, such as methyl-, ethyl-, propyl-, or butyl-paraben, benzyl-paraben; acids, such as sorbic acid, benzoic acid and its salts; quaternary ammonium compounds, such as alkonium salts, e.g. benzalkonium salts, especially the chlorides or bromides, cetrimonium salts, e.g. the bromide; phenoalkecinium salt, such as phenododecinium bromide, cetylpyridinium chloride or other such salts; mercurium compounds, such as phenylmercuric acetate, borate, or nitrate, thiomersal; chlorhexidine or its gluconate; antibiotically active compounds of biological origin, or a mixture thereof.

11. The method according to claim 10, **characterised in that** the bulk concentration of short chain alcohols in the case of ethyl, propyl, butyl or benzyl alcohol is up to 10 w-%, more preferably is up to 5 w-%, and most preferably is in the range between 0.5-3 w-%, and in the case of chlorobutanol is in the range between 0.3-0.6 w-%; bulk concentration of parabens, especially in the case of methyl paraben is in the range between 0.05-0.2 w-%, and in the case of propyl paraben is in the range between 0.002-0.02 w-%; bulk concentration of sorbic acid is in the range between 0 .05-0.2 w-%, and in the case of benzoic acid is in the range between 0.1-0.5 w-%; bulk concentration of phenols, triclosan, is in the range between 0.1-0.3 w-%, and bulk concentration of chlorhexidine is in the range between 0.01-0.05 w-%.

12. The method according to any one of the preceding claims, **characterised in that** the less soluble amongst the aggregating substances is a lipid or lipid-like material, especially a polar lipid, whereas the substance which is more soluble in the suspending liquid and which lowers the average elastic energy of the droplet is a surfactant or else has surfactant-like properties and / or is a form of said lipid or lipid-like material which is comparably as soluble as said surfactant or the surfactant-like material.

13. The method according to claim 12, **characterised in that** the lipid or lipid-like material is a lipid or a lipoid from a biological source or a corresponding synthetic lipid or any of its modifications, said lipid preferably belonging to the class of pure phospholipids corresponding to the general formula



where R_1 and R_2 is an aliphatic chain, typically a C_{10-20}-acyl, or -alkyl or partly unsaturated fatty acid residue, in particular, an oleoyl-, palmitoeloyl-, elaidoyl-, linoleyl-, linolenyl-, linolenoyl-, arachidoyl-, vaccinyl-, lauroyl-, myristoyl-, palmitoyl-, or stearoyl chain; and where R_3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C_{1-4}-alkyl, C_{1-5}-alkyl substituted with carboxy, C_{2-5}-alkyl substituted with hydroxy, C_{2-5}-alkyl substituted with carboxy and hydroxy, or C_{2-5}-alkyl substituted with carboxy and amino, inositol, sphingosine, or salts of said substances, said lipid comprising also glycerides, isoprenoid lipids, steroids, sterines or sterols, of sulphur- or carbohydrate-containing lipids, or any other bilayer-forming lipids, in particular half-protonated fluid fatty acids, said lipid is selected from the group comprising phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, phosphatidylserines, sphingomyelins or other sphingophospholipids, glycosphingolipids (including cerebrosides, ceramidepolyhexosides, sulphatides, sphingoplasmalogens), gangliosides and other glycolipids or synthetic lipids, in particular with corresponding sphingosine derivatives, or any other glycolipids, whereby two similar or different chains can be ester-groups-linked to the backbone (as in diacyl and dialkenoyl compound) or be attached to the backbone with ether bonds, as in dialkyl-lipids.

14. The method according to claim 12,

characterised in that the surfactant or surfactant-like material is a nonionic, a zwitterionic, an anionic or a cationic surfactant, especially a fatty-acid or -alcohol, an alkyl-tri/di/methyl-ammonium salt, an alkylsulphate salt, a monovalent salt of cholate, deoxycholate, glycocholate, glycodeoxycholate, taurodeoxycholate, taurocholate, etc., an acyl- or alkanoyl-dimethyl- aminoxide, esp. a dodecyl-dimethyl-aminoxide, an alkyl- or alkanoyl-N-methylglucamide, N- alkyl-N,N-dimethylglycine, 3-(acyldimethylammonio)-alkanesulphonate, N-acyl-sulphobetaine, a polyethylene-glycol-octylphenyl ether, esp. a nonaethylene-glycol-octylphenyl ether, a polyethylene-acyl ether, esp. a nonaethylen-dodecyl ether, a polyethylene-glycol-isoacyl ether, esp. a octaethylene-glycol-isotridecyl ether, polyethylene-acyl ether, esp. octaethylenedodecyl ether, polyethylene-glycol-sorbitane-acyl ester, such as polyethylenglykol-20-monolaurate (Tween 20) or polyethylenglykol-20-sorbitan-monooleate (Tween 80), a polyhydroxyethylene-acyl ether, esp. polyhydroxyethylene- lauryl, -myristoyl, -cetylstearyl, or -oleoyl ether, as in polyhydroxyethylene-4 or 6 or 8 or 10 or 12, etc., -lauryl ether (as in Brij series), or in the corresponding ester, e.g. of polyhydroxyethylen-8-stearate (Myrj 45), -laurate or -oleate type, or in polyethoxylated castor oil 40, a sorbitane-monoalkylate (e.g. in Arlacel or Span), esp. sorbitane-monolaurate, an acyl- or alkanoyl-N-methylglucamide, esp. in or decanoyl- or dodecanoyl-N-methylglucamide, an alkyl-sulphate (salt), e.g. in lauryl- or oleoyl-sulphate, sodium deoxycholate, sodium glycodeoxycholate, sodium oleate, sodium taurate, a fatty acid salt, such as sodium elaidate, sodium linoleate, sodium laurate, a lysophospholipid, such as n-octadecylene(=oleoyl)-glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-acyl-, e.g. lauryl or oleoyl-glycero-phosphatidic acid, -phosphorylglycorol, or -phosphorylserine, n-tetradecyl-glycero-phosphatidic acid, -phosphorylglycerol, or - phosphorylserine, a corresponding palmitoeloyl-, elaidoyl-, vaccenyl-lysophospholipid or a corresponding short-chain phospholipid, or else a surface-active polypeptide.

15. The method according to any of the preceding claims, **characterised in that** the average diameter of the penetrant is between 30 nm and 500 nm, more preferably between 40 nm and 250 nm, even more preferably between 50 nm and 200 nm and particularly preferably between 60 nm and 150 nm.

16. The method according to any one of the preceding claims, **characterised in that** the total dry weight of droplets in a formulation is 0.01 weight-% (w-%) to 40 w-% of total formulation mass, more preferably between 0.1 w-% and 30 w-%, and most preferably between 0,5 w-% and 20 w-%.

17. The method according to any one of the preceding claims, **characterised in that** the total dry weight of droplets in a formulation is selected to increase the formulation viscosity to maximally 200 mPas, more preferably up to 40 mPas, and most preferably up to 8 mPas.

18. The method according to any one of the preceding claims, **characterised in that** at least one amphiphilic substance and/or at least one edge-active substance or surfactant, and / or at least one hydrophilic fluid and the agent are mixed, if required separately, to form a solution, the resulting (partial) mixtures or solutions are then combined subsequently to induce, preferably by action of mechanical energy such as shaking, stirring, vibrations, homogenisation, ultrasonication, shearing, freezing and thawing, or filtration using convenient driving pressure, the formation of penetrants that associate with and / or incorporate the agent

19. The method of claim 18,

characterised in that said amphiphilic substances are dissolved in volatile solvents, such as alcohols, especially ethanol, or in other pharmaceutically acceptable organic solvents, such as ethanol, 1- and 2-propanol, benzyl alcohol, propylene glycol, polyethylene glycol (molecular weight: 200-400 D) or glycerol, other pharmaceutically acceptable organic solvents, such as undercooled gas, especially supercritical CO_2, which are then removed, especially by evaporation or dilution, prior to making the final preparation.

20. The method according to any one of claims 18 or 19, **characterised in that** the formation of said penetrants is induced by the addition of required substances into a fluid phase, evaporation from a reverse phase, by injection or dialysis, if necessary under the influence of mechanical stress, such as shaking, stirring, in especially high velocity stirring, vibrating, homogenising, ultrasonication, shearing, freezing and thawing, or filtration using convenient, in especially low (1 MPa) or intermediate (up to 10 MPa), driving pressure.

21. The method of claim 20, **characterised in that** the formation of said penetrants is induced by filtration, the filtering material having pores sizes between 0.01 µm and 0.8 µm, more preferably between 0.02 µm and 0.3 µm, and most preferably between 0.05 µm and 0.15 µm, whereby several filters may be used sequentially or in parallel.

22. The method according to any one of claims 18 to 21, **characterised in that** said agents and penetrants are made to associate, at least partly,

- after the formation of said penetrants, e.g. after injecting a solution of the drug in a pharmaceutically acceptable fluid, such as ethanol, 1- and 2-propanol, benzyl alcohol, propylene glycol, polyethylene glycol (molecular weight: 200-400 D) or glycerol into the suspending medium,

– simultaneously with penetrant formation , if required using the drug co-solution and, at least some, penetrant ingredients.

23. The method according to any one of the claims 18 to 22, **characterised in that** said penetrants, with which the agent is associated, are prepared immediately before the application of the formulation, if convenient, from a suitable concentrate or a lyophylisate.

24. The method according to any one of the preceding claims, **characterised in that** the formulation is applied by spraying, smearing, rolling or sponging on the application area, in particular by using a metering sprayer, spender, roller, sponge or a non-occlusive patch, as appropriate.

25. The method according to any one of the preceding claims, **characterised in that** the barrier is a part of a mammalian body and / or a plant and preferably is skin and / or at least partly keratinised endothelium and / or nasal or any other mucosa.

26. The method according to claim 25, **characterised in that**, the area dose of said penetrant is between 0.1 mg per square centimetre (mg cm^{-2}) and 40 mg cm^{-2}, more preferably is between 0.25 mg cm^{-2} and 30 mg cm^{-2} and even more preferably is between 0.5 mg cm^{-2} and 15 mg cm^{-2}, in case the penentrant is applied on said skin and / or said at least partly keratinised endothelium.

27. The method according to claim 25, **characterised in that** the area dose of said penetrant is between 0.05 mg per square centimetre (mg cm^{-2}) and 20 mg cm^{-2}, more preferably is between 0.1 mg cm^{-2} and 15 mg cm^{-2}) and even more preferably is between 0.5 mg cm^{-2}

and 10 mg cm^{-2}, in the case the penentrant is applied on said nasal or other mucosa.

28. The method according to claim 25,

characterised in that the area dose of said penetrant is between 0.0001 mg per square centimetre (mg cm^{-2}) and 0.1 mg cm^{-2}, more preferrably is between 0.0005 mg cm^{-2} and 0.05 mg cm^{-2} and even more preferrably is between 0.001 mg cm^{-2} and 0.01 mg cm^{-2} , in the case that the penetrant is applied on plant body, plant leaves or plant needles.

29. A kit containing said formulation in an amount which enables the formulation to be applied at the selected dose per area, according to any one of the preceding claims.

30. The kit according to claim 29,

characterised in that the formulation is contained in a bottle or any other packaging vessel.

31. The kit according to claims 29 or 30,

characterised in that it contains a device for administering the formulation.

32. A patch, containing the formulation as in any one of claims 1 to 28 in an amount that yields the dose per area according to any one of the preceding claims.

33. The patch according to claim 32,

comprising:

- a non-occlusive backing liner;

– an inner liner, wherein the backing liner and the inner liner define a reservoir; and /or a matrix layer.

34. The patch according to claims 32 or 33,
characterised in that the non-occlusive backing liner exhibits a mean vapor transmission rate (MVTR) of more than 1000 g/m²day, preferably of more than 5.000 g/m²day and most preferably of more than 10.000 g/m²day.

35. The patch according to claims 32 or 34,
characterised in that the non-occlusive backing liner has pores of smaller than 100 nm, preferably smaller than 70 nm and most preferably of smaller than 30 nm.

36. The patch according to any one of claims 32 to 35,
characterised in that the non-occlusive backing liner comprises a polyurethane membrane, preferably a polyester track-etched porous membrane, more preferably a polycarbonate track-etched porous membrane and most preferably a polyethylene microporous membrane.

37. The patch according to any one of claims 32 to 36,
characterised in that the inner liner prevents unwanted release of the formulation from the patch during storage and enables rapid skin wetting when contacted with the skin.

38. The patch according to any one of claims 32 to 37,
characterised in that the inner liner comprises a homogeneous membrane, preferably a polyester track-etched porous membrane or a polycarbonate track-etched porous membrane.

39. The patch according to claim 38,

characterised in that the membranes have a pore density of up to 5%, preferably of up to 15%, more preferably of up to 25% and most preferably of more than 25% and/or a pore size in the range between 20 nm and 200 nm, preferably between 50 nm and 140 nm and most preferably between 80 nm and 120 nm.

40. The patch according to any one of claims 32 to 39, **characterised in that** the inner liner comprises a hydrophobic mesh-membrane and/or a nonwoven fleece with mesh openings formed by hydrophobic threads.

41. The patch according to any one of claims 32 to 40, **characterised in that** the inner liner comprises a microporous polyethylene membrane having average pore sizes in the range of between 50 nm to 3000 nm, preferably between 500 nm to 2000 nm and most preferably of about 1500 nm.

42. The patch according to any one of claims 32 to 41, **characterised in that** the patch comprises a pressure sensitive adhesive layer, preferably an adhesive layer comprising polyacylate, polyisobutylene, silicone, ethylene vinyl acetate copolymer, polyvinylpyrrolidone or polyethylene oxide hydrogel.

43. The patch according to any one of claims 32 to 42, **characterised in that** the formulation viscosity is up to maximally 200 mPas, more preferably up to 40 mPas, and most preferably up to 8 mPas.

44. The patch according to any one of claims 32 to 43, **characterised in that** the patch comprises one or more additional layers comprising desiccant containing layers, matrix layers, foam tape layers and/or protective layers.

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45. The patch according to claim 32 to 44,
characterised in that the patch comprises at least two compartments, which are separated from each other during storage.

46. The patch according to claim 32 to 45,
characterised in that at least one of the compartments is inside and / or outside the patch.

47. The patch according to claim 32 to 46,
characterised in that the formulation and / or the individual formulation components and/or the agent and / or the suspension / dispersion of penetrants without the agent are kept during the storage in several, preferably less than 5, more preferably in 3, and most preferred in 2 separate compartments of the patch which, in case, are combined prior to or during or after the application of the patch.

48. The patch according to claim 32 to 47,
characterised in that the outer compartment(s) comprise(s) injection systems, which are connected to the reservoir.

49. The patch according to claim 32 to 47,
characterised in that the compartments are inside the reservoir, which is defined by the backing liner and the inner liner.

50. The patch according to claim 32 to 47,
characterised in that the compartments are vertically stacked and /or are arranged side-by-side and / or one compartment is included in a second compartment, preferably without being fixed to the second compartment.

51. The patch according to claim 49 or 50,
characterised in that the compartments are separated from each other by a controllably openable barrier, preferably a membrane and /or by a plug and / or by a compartment-forming lamination.

52. The patch according to claim 45 to 51,
characterised in that combining and mixing of the ingredients of the compartments is achieved by direct mechanical action, such as pressing, rubbing, kneading, twisting, tearing and /or indirectly by changing the temperature, osmotic pressure or electrical potential.

53. The patch according to claim 32,
comprising:
- a non-occlusive backing liner as in any of claims 34 to 37
- a membrane defining a reservoir, which is divided in at least two compartments,

characterised in that the formulation directly contacts the skin when the formulation releases from the reservoir.

54. A method of administering an agent to a mammalian body or a plant, by transporting said agent through a barrier, wherein the barrier is the intact skin, mucosa and/or cuticle of said mammalian body or a plant, said agent being associated to a penetrant capable of transporting said agent through the skin pores or through the passages in mucosa or cuticle, or capable of enabling agent permeation through skin pores after said penetrant has opened and/or entered said pores, comprising the steps of:
- preparing a formulation by suspending or dispersing said penetrants in a polar liquid in the form of fluid droplets surrounded by a membrane-like coating of

one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate, provided that

- said at least two substances differ by at least a factor of 10 in solubility in said polar liquid,
- and / or said substances when in the form of homo-aggregates (for the more soluble substance) or of hetero-aggregates (for any combination of both said substances) have a preferred average diameter smaller than the diameter of homo-aggregates containing merely the less soluble substance,
- and / or the more soluble substance tends to solubilise the droplet and the content of such substance is to up to 99 mol-% of solubilising concentration or else corresponds to up to 99 mol-% of the saturating concentration in the unsolubilised droplet, whichever is higher,
- and / or the presence of the more soluble substance lowers the average elastic energy of the membrane-like coating to a value at least 5 times lower, more preferably at least 10 times lower and most preferably more than 10 times lower, than the average elastic energy of red blood cells or of phospholipid bilayers with fluid aliphatic chains,
- said penetrants being able to transport agents through the pores of said barrier or being able to promote agent permeation through the pores of said skin after penetrants have entered the pores,
- selecting a dose amount of said penetrants to be applied on a predetermined area of said barrier to control the flux of said penetrants across said barrier, and
- applying the selected dose amount of said formulation containing said penetrants onto said area of said porous barrier.

55. The method according to claim 54,

characterised in that the flux of penetrants across said barrier is increased by enlarging the applied dose per area of said penetrants.

56. The method according to claims 54 or 45, **characterised in that** the pH of the formulation is between 3 and 10, more preferably between 4 and 9, and most preferably between 5 and 8.

57. The method according to claims 54 to 56, **characterised in that** the formulation comprises:

- at least one thickening agent in an amount that increases the formulation viscosity to maximally 5 Nm/s, more preferably up to 1 Nm/s, and most preferably up to 0.2 Nm/s, so that formulation spreading-over, and drug retention at the application area is enabled,
- and / or at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100 % per 6 months, more preferably to less than 100 % per 12 months and most preferably to less than 50 % per 12 months
- and / or at least one microbicide in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days.

58. Method according to claim 54, **characterised in that** said at least one microbicide is added in an amount that reduces the bacterial count of 1 million germs added per g of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 3 days, and more preferably after a period of 1 day.

59. The method according to claim 54,

characterised in that said thickening agent is selected from the class of pharmaceutically acceptable hydrophilic polymers, such as partially etherified cellulose derivatives, like carboxymethyl-, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl- or methyl-cellulose; completely synthetic hydrophilic polymers such as polyacrylates , polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylates, polyacrylonitriles, methallyl-sulphonates, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactides, polyethylene glycol-diacrylates, polyvinylpyrrolidones, polyvinyl alcohols, poly(propylmethacrylamides), poly(propylene fumarate-co-ethylene glycols), poloxamers, polyaspartamides, (hydrazine cross-linked) hyaluronic acids, silicones; natural gums comprising alginates, carrageenans, guar-gums, gelatines, tragacanths, (amidated) pectins, xanthans, chitosan collagens, agaroses; mixtures and further derivatives or co-polymers thereof and / or other pharmaceutically, or at least biologically, acceptable polymers.

60. The method according to claim 59,
characterised in that the concentration of said polymer is in the range between 0.01 w- % and 10 w- %, more preferably in the range between 0.1 w- % and 5 w- %, even more preferably in the range between 0.25 w- % and 3.5 w- % and most preferably in the range between 0.5 w- % and 2 w- %.

61. The method according to claim 54,
characterised in that said anti-oxidant is selected from synthetic phenolic antioxidants, such as butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX, etc.), tertiary butylhydroquinone (TBHQ), propyl gallate (PG), 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ); aromatic amines (such as diphenylamine, p-alkylthio-o-anisidine, ethylenediamine

derivatives, carbazol, tetrahydroindenoindol); phenols and phenolic acids (such as guaiacol, hydroquinone, vanillin, gallic acids and their esters, protocatechuic acid, quinic acid, syringic acid, ellagic acid , salicylic acid, nordihydroguaiaretic acid (NDGA), eugenol); tocopherols (including tocopherols (alpha, beta, gamma, delta) and their derivatives, such as tocopheryl-acylate (e.g. -acetate, -laurate, myristate, -palmitate, -oleate, -linoleate, etc., or any other suitable tocopheryl-lipoate), tocopheryl-POE-succinate; trolox and corresponding amide- and thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters (e.g. 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid, etc.); non-steroidal anti-inflammatory agents (NSAIDs), such as indomethacin, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofen, ketoprofen, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital, acetaminephen); aminosalicylic acids and derivatives; methotrexate, probucol, antiarrhythmics (e.g. amiodarone, aprindine, asocainol), ambroxol, tamoxifen, b-hydroxytamoxifen; calcium antagonists (such as nifedipine, nisoldipine, nimodipine, nicardipine, nilvadipine), beta-receptor blockers (e.g. atenolol, propranolol, nebivolol); sodium bisulphite, sodium metabisulphite, thiourea; chelating agents, such as EDTA, GDTA, desferral; endogenous defence systems, such as transferrin, lactoferrin, ferritin, cearuloplasmin, haptoglobion, haemopexin, albumin, glucose, ubiquinol-10; enzymatic antioxidants, such as superoxide dismutase and metal complexes with a similar activity, including catalase, glutathione peroxidase, and less complex molecules, such as beta-carotene, bilirubin, uric acid; flavonoids (e.g. flavones, flavonols, flavonones, flavanonals, chacones, anthocyanins), N-acetylcystein, mesna, glutathione, thiohistidine derivatives, triazoles; tannines, cinnamic acid, hydroxycinnamatic acids and their esters (e.g. coumaric acids and esters, caffeic acid and their esters, ferulic acid, (iso-) chlorogenic acid, sinapic acid); spice

extracts (e.g. from clove, cinnamon, sage, rosemary, mace, oregano, allspice, nutmeg); carnosic acid, carnosol, carsolic acid; rosmarinic acid, rosmarindiphenol, gentisic acid, ferulic acid; oat flour extracts, such as avenanthramide 1 and 2; thioethers, dithioethers, sulphoxides, tetralkylthiuram disulphides; phytic acid, steroid derivatives (e.g. U74006F); tryptophan metabolites (e.g. 3-hydroxykynurenine, 3-hydroxyanthranilic acid), and organochalcogenides, or else is an oxidation suppressing enzyme.

62. The method according to claim 54, **characterised in that** the concentration of BHA or BHT is between 0.001 and 2 w-%, more preferably is between 0.0025 and 0.2 w-%, and most preferably is between 0.005 and 0.02 w-%, of TBHQ and PG is between 0.001 and 2 w-%, more preferably is between 0.005 and 0.2 w-%, and most preferably is between 0.01 and 0.02 w-%, of tocopherols is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.075 w-%, of ascorbic acid esters is between 0.001 and 5, more preferably is between 0.005 and 0.5, and most preferably is between 0.01 and 0.15 w-%, of ascorbic acid is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.1 w-%, of sodium bisulphite or sodium metabisulphite is between 0.001 and 5, more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01-0.15 w-%, of thiourea is between 0.0001 and 2 w-%, more preferably is between 0.0005 and 0.2, and most preferably is between 0.001–0.01 w-%, most typically 0.005 w-%, of cystein is between 0.01 and 5, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1 and 1.0 w-%, most typically 0.5 w-%, of monothioglycerol is between 0.01 and 5 w-%, more preferably is between 0.05 and 2 w-%, and most preferably is between 0.1-1.0 w-%, most typically 0.5 w-%, of NDGA is between 0.0005-2 w-%, more preferably is between 0.001–0.2 w-%, and most preferably is between 0.005-0.02 w-%, most typically 0.01 w-%, of

glutathione is between 0.005 and 5 w-%, more preferably is between 0.01 and 0.5 w-%, and most preferably is between 0.05 and 0.2 w-%, most typically 0.1 w-%, of EDTA is between 0.001 and 5 w-%, even more preferably is between 0.005 and 0.5 w-%, and most preferably is between 0.01 and 0.2 w-%, most typically between 0.05 and 0.975 w-%, of citric acid is between 0.001 and 5 w-%, even more preferably is between 0.005 and 3 w-%, and most preferably is between 0.01-0.2, most typically between 0.3 and 2 w-%.

63. The method according claim 54,

characterised in that said microbicide is selected amongst short chain alcohols, such as ethyl and isopropyl alcohol, chlorbutanol, benzyl alcohol, chlorbenzyl alcohol, dichlorbenzylalcohol; hexachlorophene; phenolic compounds, such as cresol, 4-chloro-m-cresol, p-chloro-m-xylenol, dichlorophene, hexachlorophene, povidon-iodine; parabens, especially alkyl-paraben, such as methyl-, ethyl-, propyl-, or butyl-paraben, benzyl-paraben; acids, such as sorbic acid, benzoic acid and its salts; quaternary ammonium compounds, such as alkonium salts, e.g. benzalkonium salts, especially the chlorides or bromides, cetrimonium salts, e.g. the bromide; phenoalkecinium salt, such as phenododecinium bromide, cetylpyridinium chloride or other such salts; mercurium compounds, such as phenylmercuric acetate, borate, or nitrate, thiomersal; chlorhexidine or its gluconate; antibiotically active compounds of biological origin, or a mixture thereof.

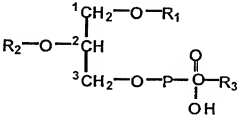
64. The method according claim 63,

characterised in that the bulk concentration of short chain alcohols in the case of ethyl, propyl, butyl or benzyl alcohol is up to 10 w-%, more preferably is up to 5 w-%, and most preferably is in the range between 0.5-3 w-%, and in the case of chlorobutanol is in the range between 0.3-0.6 w-%; bulk concentration of parabens, especially in the case of methyl paraben is in the range between

0.05-0.2 w-%, and in the case of propyl paraben is in the range between 0.002-0.02 w-%; bulk concentration of sorbic acid is in the range between 0 .05-0.2 w-%, and in the case of benzoic acid is in the range between 0.1-0.5 w-%; bulk concentration of phenols, triclosan, is in the range between 0.1-0.3 w-%, and bulk concentration of chlorhexidine is in the range between 0.01-0.05 w-%.

65. The method according to claims 54 to 64, **characterised in that** the less soluble amongst the aggregating substances is a lipid or lipid-like material, especially a polar lipid, whereas the substance which is more soluble in the suspending liquid and which lowers the average elastic energy of the droplet is a surfactant or else has surfactant-like properties and / or is a form of said lipid or lipid-like material which is comparably soluble as said surfactant or the surfactant-like material.

66. The method according to claim 65, **characterised in that** the lipid or lipid-like material is a lipid or a lipoid from a biological source or a corresponding synthetic lipid or any of its modifications, said lipid preferably belonging to the class of pure phospholipids corresponding to the general formula



where R_1 and R_2 is an aliphatic chain, typically a C_{10-20}-acyl, or -alkyl or partly unsaturated fatty acid residue, in particular, an oleoyl-, palmitoeloyl-, elaidoyl-,

linoleyl-, linolenyl-, linolenoyl-, arachidoyl-, vaccinyl-, lauroyl-, myristoyl-, palmitoyl-, or stearoyl chain; and where R_3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C_{1-4}-alkyl, C_{1-5}-alkyl substituted with carboxy, C_{2-5}-alkyl substituted with hydroxy, C_{2-5}-alkyl substituted with carboxy and hydroxy, or C_{2-5}-alkyl substituted with carboxy and amino, inositol, sphingosine, or salts of said substances, said lipid comprising also glycerides, isoprenoid lipids, steroids, sterines or sterols, of sulphur- or carbohydrate-containing lipids, or any other bilayer-forming lipids, in particular half-protonated fluid fatty acids, said lipid is selected from the group comprising phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, phosphatidylserines, sphingomyelins or other sphingophospholipids, glycosphingolipids (including cerebrosides, ceramidepolyhexosides, sulphatides, sphingoplasmalogens), gangliosides and other glycolipids or synthetic lipids, in particular with corresponding sphingosine derivatives, or any other glycolipids, whereby two similar or different chains can be ester-groups-linked to the backbone (as in diacyl and dialkenoyl compound) or be attached to the backbone with ether bonds, as in dialkyl-lipids.

67. The method according to claim 65,

characterised in that the surfactant or surfactant-like material preferrably is a nonionic, a zwitterionic, an anionic or a cationic surfactant, especially a fatty-acid or -alcohol, an alkyl-tri/di/methyl-ammonium salt, an alkylsulphate salt, a monovalent salt of cholate, deoxycholate, glycocholate, glycodeoxycholate, taurodeoxycholate, taurocholate, etc., an acyl- or alkanoyl-dimethyl- aminoxide, esp. a dodecyl- dimethyl-aminoxide, an alkyl- or alkanoyl-N-methylglucamide, N-alkyl-N,N- dimethylglycine, 3-(acyldimethylammonio)-alkanesulphonate, N-acyl-sulphobetaine, a polyethylene-glycol-octylphenyl ether, esp. a nonaethylene-glycol-octylphenyl ether, a polyethylene-acyl ether, esp. a nonaethylen-dodecyl ether, a polyethylene-glycol-isoacyl ether, esp. a octaethylene-glycol-isotridecyl

ether, polyethylene-acyl ether, esp. octaethylenedodecyl ether, polyethylene-glycol-sorbitane-acyl ester, such as polyethylenglykol-20-monolaurate (Tween 20) or polyethylenglykol-20-sorbitan-monooleate (Tween 80), a polyhydroxyethylene-acyl ether, esp. polyhydroxyethylene- lauryl, -myristoyl, -cetylstearyl, or -oleoyl ether, as in polyhydroxyethylene-4 or 6 or 8 or 10 or 12, etc., -lauryl ether (as in Brij series), or in the corresponding ester, e.g. of polyhydroxyethylen-8-stearate (Myrj 45), -laurate or -oleate type, or in polyethoxylated castor oil 40, a sorbitane-monoalkylate (e.g. in Arlacel or Span), esp. sorbitane-monolaurate, an acyl- or alkanoyl-N-methylglucamide, esp. in or decanoyl- or dodecanoyl-N-methylglucamide, an alkyl-sulphate (salt), e.g. in lauryl- or oleoyl-sulphate, sodium deoxycholate, sodium glycodeoxycholate, sodium oleate, sodium taurate, a fatty acid salt, such as sodium elaidate, sodium linoleate, sodium laurate, a lysophospholipid, such as n-octadecylene(=oleoyl)-glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-acyl-, e.g. lauryl or oleoyl-glycero-phosphatidic acid, -phosphorylglycorol, or -phosphorylserine, n-tetradecyl-glycero-phosphatidic acid, -phosphorylglycerol, or - phosphorylserine, a corresponding palmitoeloyl-, elaidoyl-, vaccenyl-lysophospholipid or a corresponding short-chain phospholipid, or else a surface-active polypeptide.

68. The method according to claims 54 to 67, **characterised in that** the average diameter of the penetrant is between 30 nm and 500 nm, more preferably between 40 nm and 250 nm, even more preferably between 50 nm and 200 nm and particularly preferably between 60 nm and 150 nm.

69. The method according to claims 54 to 68, **characterised in that** the total dry weight of droplets in a formulation is 0.01 weight-% (w-%) to 40 w-% of total formulation mass, more preferably between 0.1 w-% and 30 w-%, and most preferably between 0,5 w-% and 20 w-%.

70. The method according to claims 54 to 69, **characterised in that** the total dry weight of droplets in a formulation is selected to increase the formulation viscosity to maximally 200 mPas, more preferably up to 40 mPas, and most preferably up to 8 mPas.

71. The method according to claims 54 to 70, **characterised in that** at least one edge-active substance or surfactant and/or at least one amphiphilic substance, and / or at least one hydrophilic fluid and the agent are mixed, if required separately, to form a solution, the resulting (partial) mixtures or solutions are then combined subsequently to induce, preferably by action of mechanical energy such as shaking, stirring, vibrations, homogenisation, ultrasonication, shearing, freezing and thawing, or filtration using convenient driving pressure, the formation of penetrants that associate with and / or incorporate the agent

72. The method according to claim 71, **characterised in that** said amphiphilic substances are dissolved in volatile solvents, such as alcohols, especially ethanol, or in other pharmaceutically acceptable organic solvents, such as ethanol, 1- and 2-propanol, benzyl alcohol, propylene glycol, polyethylene glycol (molecular weight: 200-400 D) or glycerol, other pharmaceutically acceptable organic solvents, such as undercooled gas, especially supercritical CO_2, which are then removed, especially by evaporation or dilution, prior to making the final preparation.

73. The method according to any one of claims 68 or 72, **characterised in that** the formation of said penetrants is induced by the addition of required substances into a fluid phase, evaporation from a reverse phase, by injection or dialysis, if necessary under the influence of mechanical stress, such as

shaking, stirring, especially high velocity stirring, vibrating, homogenising, ultrasonication, shearing, freezing and thawing, or filtration using a convenient, especially low (1 MPa) or intermediate (up to 10 MPa), driving pressure.

74. The method according to claim 73, **characterised in that** the formation of said penetrants is induced by filtration, the filtering material having pores sizes between 0.01 μm and 0.8 μm, more preferably between 0.02 μm and 0.3 μm, and most preferably between 0.05 μm and 0.15 μm, whereby several filters may be used sequentially or in parallel.

75. The method according to any one of claims 55 to 74, **characterised in that** said agents and penetrants are made to associate, at least partly,

- after the formation of said penetrants, e.g. after injecting a solution of the drug in a pharmaceutically acceptable fluid, such as ethanol, 1- and 2-propanol, benzyl alcohol, propylene glycol, polyethylene glycol (molecular weight: 200-400 D) or glycerol into the suspending medium,
- simultaneously with penetrant formation , if required using the drug co-solution and, at least some, penetrant ingredients.

76. The method according to any one of the claims 55 to 75, **characterised in that** said penetrants, with which the agent is associated, are prepared immediately before the application of the formulation, if convenient, from a suitable concentrate or a lyophylisate.

77. The method according to any one of the claims 55 to 76, **characterised in that** the formulation is applied by spraying, smearing, rolling or sponging on the application area, in particular by using a metered sprayer, spender, roller or a sponge, or a non-occlusive patch, as appropriate.

78. The method according to any one of the claims 55 to 77, **characterised in that** the barrier is skin or at least partly keratinised endothelium and / or nasal or any other mucosa.

79. The method according to claim 78, **characterised in that,** the area dose of said penetrant is between 0.1 mg per square centimetre (mg cm^{-2}) and 40 mg cm^{-2}, more preferably is between 0.25 mg cm^{-2} and 30 mg cm^{-2} and even more preferably is between 0.5 mg cm^{-2} and 15 mg cm^{-2}, in the case that the penentrant is applied on said skin and / or said at least partly keratinised endothelium.

80. The method according to claim 78, **characterised in that** the area dose of said penetrant is between 0.05 mg per square centimetre (mg cm^{-2}) and 20 mg cm^{-2}, more preferably is between 0.1 mg cm^{-2} and 15 mg cm^{-2} and even more preferably is between 0.5 mg cm^{-2} and 10 mg cm^{-2}, in the case that the penentrant is applied on said nasal or other mucosa.

81. The method according to claim 78, **characterised in that** the area dose of said penetrant is between 0.0001 mg per square centimetre (mg cm^{-2}) and 0.1 mg cm^{-2}, more preferrably is between 0.0005 mg cm^{-2} and 0.05 mg cm^{-2} and even more preferrably is between 0.001 mg cm^{-2} and 0.01 mg cm^{-2} ,in the case that the penetrant is applied on plant body, plant leaves or plant needles.

82. The method of claim 54, used for generating an immune response on a human or other mammal by vaccinating said mammal.

83. The method of claim 54, used for generating a therapeutic effect in a human or other mammal.

84. The method of claim 54 for the treatment of inflammatory disease, dermatosis, kidney or liver failure, adrenal insufficiency, aspiration syndrome, Behcet syndrome, bites and stings, blood disorders, such as cold-haemagglutinin disease, haemolytic anemia, hypereosinophilia, hypoplastic anemia, macroglobulinaemia, trombocytopenic purpura, furthermore, for the management of bone disorders, cerebral oedema, Cogan´s syndrome, congenital adrenal hyperplasia, connective tissue disorders, such as lichen, lupus erythematosus, polymyalgia rheumatica, polymyositis and dermatomyositis, epilepsy, eye disorders, such as cataracts, Graves´ ophthalmopathy, haemangioma, herpes infections, neuropathies, retinal vasculitis, scleritis, for some gastro-intestinal disorders, such as inflammatory bowel disease, nausea and oesophageal damage, for hypercalcaemia, infections, e.g. of the eye (as in infections mononucleosis), for Kawasaki disease, myasthenia gravis, various pain syndromes, such as postherpetic neuralgia, for polyneuropathies, pancreatitis, in respiratory disorders, such as asthma, for the management of rheumatoid disease and osteoarthritis, rhinitis, sarcoidosis, skin diseases, such as alopecia, eczema, erythema multiforme, lichen, pemphigus and pemphigoid, psoriasis, pyoderma gangrenosum, urticaria, in case of thyroid and vascular disorders.